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Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review

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Ibogaine is an indole alkaloid derived from the bark of the root of the African shrub *Tabernanthe iboga*. Psychoactive properties of ibogaine have been known for decades. More recently, based on experimental data from animals and anecdotal reports in human, it has been found that this drug has anti-addictive effects. Several patents were published between 1969 and 1995. The pharmacology of ibogaine is quite complex, affecting many different neurotransmitter systems simultaneously. However, the pharmacological targets underlying the

physiological and psychological actions of ibogaine are not completely understood. Ibogaine is rapidly metabolized in the body in noribogaine. The purpose of this article was to review data from the literature concerning physicochemical properties, bio-analytical methods, and pharmacology of ibogaine; this article will be focused on the use of this drug as anti-addictive agent.

Key words: bioanalytical methods; ibogaine; noribogaine; pharmacodynamic studies; pharmacokinetics; safety

Introduction

The development process of the medicinal product is a system consisting of many operational aspects designed to solve certain organizational, scientific, and regulatory questions.^{1,2} Ideally one can have a clear view about this system, meet the needs, and have a product on the market. The real problems are the practicalities that hinder implementation of ideal principles and make product failed. Bibliographical review of ibogaine development might be one of the learning case studies that we can learn from others. Ibogaine is one of the psychoactive indole alkaloids naturally occurring in the West African shrub *Tabernanthe iboga*. The major components of *T. iboga* root bark extracts are ibogaine (approximately 80%), ibogaline (15%), and ibogamine (up to 5%), which confirms the complexity of the extract.³ From the results of the preclinical studies and anecdotal reports from American and European addict self-help groups, ibogaine could be a promising drug in addiction therapy. Unfortunately, lost opportunities to confirm a positive benefit risk balance during both preclinical and clinical developments as well as losses of financial supports have lead to the stopping of the ibogaine development in the treatment of drug dependence. Future will show the strategy one will obtain and outcome thereof –

will we forget about this novelty in addictive therapy or will we have a finalized development.

The mechanism of action of ibogaine in the treatment of drug addiction appears to be distinct from other existing pharmacotherapeutic approaches. The purpose of this article was to review data from the literature concerning physicochemical properties, bio-analytical methods, and pharmacology of ibogaine; this article will be focused on the use of this drug as anti-addictive agent.

To identify articles for this review, we use Internet-based Grateful Med to access electronic databases: MEDLINE and Currents Contents 1957–2007. We searched, without language limitations, for the subject terms “ibogaine”, “noribogaine”, “mechanism of action”, “quantification”, “pharmacokinetics”, and “pharmacodynamics”. We further narrowed the search by using the terms “anti-addictive properties”, “animals”, “healthy volunteers”, and “dependent patients”. We then improved the search using the terms “withdrawal signs” and “drug craving”. We identified additional citations from the reference sections of articles retrieved and consulted these articles. We completed this search using the website “google.com” and the engine “Copernic”.

History

Ibogaine is a naturally occurring plant indole alkaloid. The root bark of the Apocynaceous shrub *T. iboga* is the most frequently cited source of

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ibogaine. The Iboga tree is the central pillar of the *Bwiti* religion practiced in West-Central Africa, mainly Gabon, Cameroon, and the Republic of the Congo, which uses the alkaloid-containing roots of the plant for its psychoactive properties in a number of ceremonies. Ibogaine is also used by indigenous peoples in low doses to combat fatigue, hunger, and thirst.⁴ Other sources of ibogaine are *Voacanga thouarsii* var. *Ortusa*,⁵ *Tabernaemontana australis*,⁶ and *Tabernaemontana orientalis*.⁷ Although known for many centuries for tribes in West Africa, research of ibogaine started in late 19th century. The first description of *T. iboga* is published in 1985 from specimens of the plant brought to France from Gabon.⁸ A published description of the ceremonial use of *T. iboga* in Gabon appears in 1885.⁹ Ibogaine was first extracted and crystallized from the *T. iboga* root in 1901.^{10–12} Ibogaine structure has been established in 1957 through chemical studies,¹³ and X-ray crystallographic investigations have fixed the configuration of the ethyl group.¹⁴ Moreover, ¹³C nuclear magnetic resonance data¹⁵ were reported in comparison with several iboga similar structures. The total synthesis of ibogaine and its availability in the form of the racemate was reported in 1966.¹⁶

The interest of ibogaine to contemporary pharmacology is that this drug possesses anti-addictive properties. Between 1969 and 1995, the anti-addictive properties of ibogaine and its use in the treatment of heroin, cocaine, amphetamine abuse, alcohol, and nicotine dependence, and even some drug abuse have been patented in the United States and in France. A French patent for the psychotherapeutic use of ibogaine at a dosage of 4–5 mg/kg was published in 1969.¹⁷ US patents have been published by Lotsof for the use of ibogaine in opioid withdrawal, dependence on cocaine and other stimulants, alcohol, nicotine, and polysubstance abuse.^{18–22} These patents claim that an oral or rectal 4–25 mg/kg dose of ibogaine interrupts addictive drug behavior for a period of 6–36 months.

Chemistry

Ibogaine (12-methoxyibogamine, (6R, 6aS, 7S, 9R)-7-ethyl-2-methoxy-6, 6a, 7, 8, 9, 10, 12, 13-octahydro-5H-6, 9-methanopyrido[1',2':1,2]azepino[4,5-*b*]indole) has a molecular weight of 310.44 (Figure 1). Extraction of ibogaine from *T. iboga* shrub requires professional training. Mainly haloalkanes or alcohols were used for extraction. Chromatography was the method of choice for its purification. Extraction of ibogaine from *T. iboga* root bark using diluted vinegar and ammonia was described.³ This drug can also be obtained semisynthetically from voacangine³ or syn-

thetically from nicotinamide by way of a 13 or 14 step process,²³ although extraction from the iboga root is a simpler method for obtaining the compound. Ibogaine has a melting point of 153 °C and a pK_a of 8.1 in 80% methylcellosolve; its heptane/water partition coefficient of 28 confirms the lipophilicity of the compound. Recently, a structural analysis of ibogaine and of its main active metabolite, noribogaine (or 12-hydroxyibogamine, (6R, 6aS, 7S, 9R)-7-ethyl-6, 6a, 7, 8, 9, 10, 12, 13-octahydro-5H-6, 9-methanopyrido[1',2':1,2]azepino[4,5-*b*]indol-2-ol, Figure 1), using Fourier transform-infrared spectroscopy, 1D and 2D nuclear magnetic resonance spectroscopy, and liquid chromatography-electrospray mass spectrometry (LC/ESI-MS) has been published.²⁴ In accordance with the article of Taylor,²⁵ a fragmentation pattern in LC/ESI-MS is proposed (Figure 2). Ibogaine and noribogaine in solution suffer facile autoxidation under light- and heat-exposure giving iboluteine and ibochine, and desmethoxyiboluteine and desmethoxyibochine, respectively.^{24–26} Recently, it has been shown that at 20 °C with daylight exposure, ibogaine (22.4 ng/mL) and noribogaine (25 ng/mL) showed a monoexponential decrease in drug concentrations; the corresponding half-lives were 81.5 min for ibogaine and 11 min for noribogaine.²⁷

Analytical methods

Ibogaine was determined in complex mixtures of *T. iboga* and in biological matrices (brain homogenate, urine, and plasma) by spectrophotometry,²⁸ thin-layer chromatography,²⁹ or gas chromatography with flame ionization,^{29–31} nitrogen-specific³² or mass-spectrometric (electron impact or chemical ionization)^{32–35} detection. Most of these methods involved a derivatization procedure. A method for determining opiate agonists including ibogaine by liquid chromatography-atmospheric-pressure chemical-ionization mass spectrometry procedure has been also described (LC/APCI-MS).³⁶ Recently, a high performance liquid chromatography method with fluo-

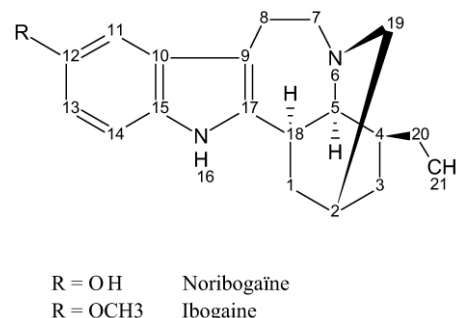


Figure 1 Molecular structures of ibogaine and noribogaine.

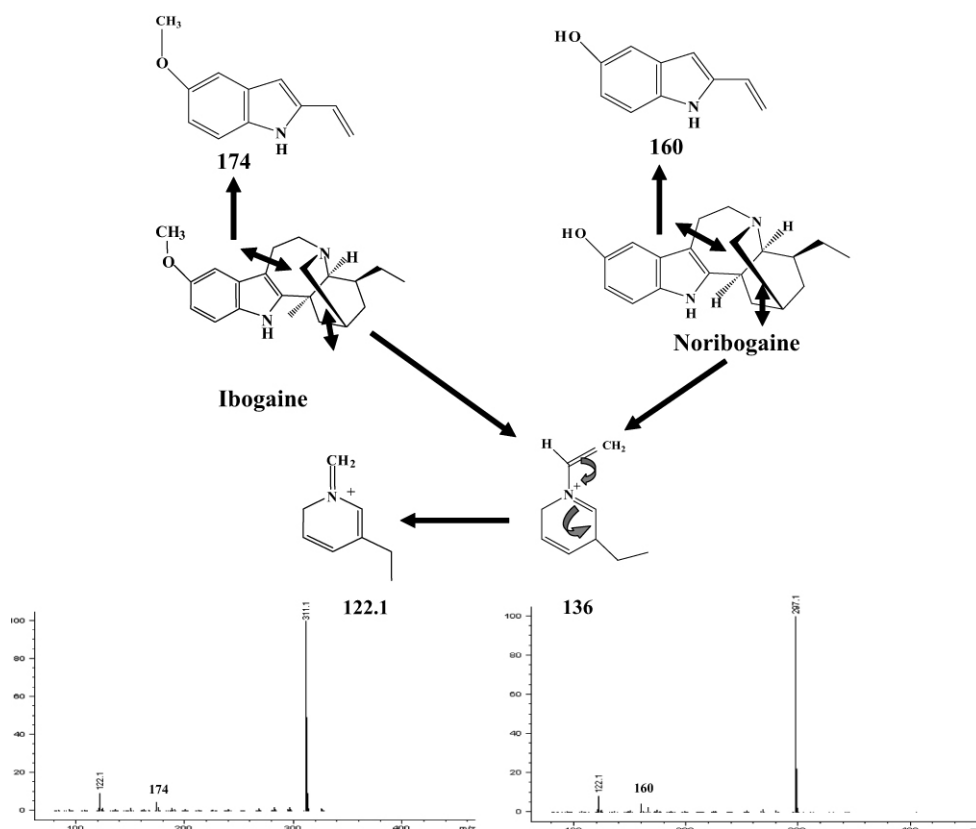


Figure 2 Fragmentation pattern of ibogaine and noribogaine.

rescence detection²⁷ and LC-MS methods with electrospray ionization^{37,38} have been published to quantify ibogaine in plasma, blood, and urine. These methods involved liquid-liquid or solid-phase extraction of the biological samples. Some of them reported simultaneous quantitation of ibogaine and its 12-hydroxy metabolite^{27,34,35,37,38}. The main characteristics of these methods are summarized in Table 1.

Formulations

In traditional use, ibogaine was consumed by chewing the root bark of *T. iboga*. Commercially available formulations include plant extracts and crystalline ibogaine hydrochloride salt. From 1901 to 1905, ibogaine was recommended as a treatment for “asthenia” at a dosage range of 10–30 mg/day. Tablets from extracts of the roots of *Tabernanthe manii*, containing about 200 mg of extract or 8 mg of ibogaine per tablet, were sold in France as a neuromuscular stimulant between 1939 and 1970 under the trade name of Lambarene®. This marketed formulation was recommended in the treatment of fatigue, depression, and recovery from infectious disease.⁹ Another ibogaine containing preparation was Iper-ton®, used as a tonic or stimulant, delivering 40 mg

of the total *T. iboga* extract.³⁹ The ibogaine hydrochloride salt (98% purity) was favored for research. Capsules containing 100 or 200 mg of ibogaine were available.⁴⁰

Most of preclinical experimentations have been reported by laboratories preparing the administered dose from the ibogaine hydrochloride acquired from Sigma Chemical Co. (compound No. I-7003, St. Louis, Mo, USA). Future research will permit the acquisition of ibogaine salt from the National Institute of Drug Abuse (NIDA). The use of ibogaine in the form of Endabuse®, the trademarked procedure to synthesize ibogaine for use in human drug abusers, provided another source for the compound. Three formulations containing ibogaine (the Sigma compound, the NIDA compound, and Endabuse®) were tested in rat for their discriminative dose-response effects. Results indicated that these drugs were equipotent.⁴¹

The main metabolite of ibogaine was noribogaine (Figure 1). Noribogaine may selectively mediate putative anti-addictive effects that persist for prolonged periods of time. Evaluation of pharmacokinetics and metabolism peculiarities of ibogaine supports the possibility of development of a slow

Table 1 Analytical methods used for the determination of ibogaine and noribogaine in biological fluids

References	Analytes	Methods		Analytical column	Extraction	LLOQ	Extraction recovery, %
		Chromatography	Matrix				
Dhahir, <i>et al.</i> ²⁸	Ibogaine	Identification TLC Silica G and UV spectra $\lambda_{\text{max}} = 278 \text{ nm}$ $\lambda_{\text{min}} = 248 \text{ nm}$	Urine Blood Tissue	—	Liquid–liquid Petroleum ether pH 10–11; back- extraction with 0.5 N HCL	—	—
Bertol, <i>et al.</i> ²⁹	Ibogaine	Identification TLC Silica 60 GC-FID	Urine	1% SE-30 silanized on Chromosorb W; 80–100 mesh (2 m)	Liquid–liquid Ether pH 12 after purification with 0.1 N HCL (pH 1)	—	—
Cartoni and Giarusso ³¹	Ibogaine	Quantitation TLC-cellulose GC-FID	Urine	1% SE-30 silanized on Chromosorb W 0.1% SE-30 on silanized glass beads; 80–100 mesh (1.80 m, 3 mm I.D.)	Liquid–liquid Ether pH 12–14 after purification with HCL pH 1	LLOD TLC: 1 µg LLOD GC: 0.05 µg	—
Gallagher, <i>et al.</i> ³²	Ibogaine	Quantitation GC-EI-MS	Tissue	DB-5 (30 m × 0.25 mm I.D.); film thickness, 0.1 µm	Liquid–liquid n-Hexane 10 N KOH; back- extraction with 0.01 N HCL	LLOD: 180 ng/g	98%
Hearn, <i>et al.</i> ³⁴	Ibogaine Noribogaine	Quantitation GC-MS	Plasma Urine Blood Tissue Plasma	DB-5 (15 m × 0.25 mm I.D.); film thickness 0.1 µm	Liquid–liquid Ethyl acetate pH > 10 Derivatization	5–10 ng/g	80–90%
Albargues, <i>et al.</i> ³⁵	Ibogaine Noribogaine	Quantitation GC-CI-MS	Plasma	DB-1 (15 m × 0.32 mm I.D.); film thickness 0.25 µm	Liquid–liquid n-butyl chloride/acetonitrile pH 13 Derivatization	10 ng/mL	Ibogaine: 55 % Noribogaine: 14%
Ley, <i>et al.</i> ³³	Ibogaine	Quantitation GC-CI-MS	Plasma	DB-1 (30 m × 0.25 mm I.D.); film thickness 0.25 µm	Solid–liquid C18 Bond – Elut cartridge; elution with methanol	1–3 ng/mL	ND
Bogusz, <i>et al.</i> ³⁶	Ibogaine	Quantitation LC-APCI-MS	Serum Urine Blood Tissue Bile Plasma	Superspher RP 18 (125 mm × 3 mm I.D.); particle size 4 µm	Solid–liquid C18 Bond – Elut cartridge; elution with methanol/ acetic acid	1 ng/mL	96%
Kontrimavičiūtė, <i>et al.</i> ²⁷	Ibogaine Noribogaine	Quantitation HPLC, fluorimetric detection	Plasma	Supelcosil C18 (75 mm × 4.6 mm I.D.); particle size, 3 µm	Solid–liquid Oasis-HLB cartridge after protein precipitation; elution with methanol	Ibogaine: 0.89 ng/mL Noribogaine: 1 ng/mL	Ibogaine: 94.2 % Noribogaine: 96.2 %
Kontrimavičiūtė, <i>et al.</i> ³⁷	Ibogaine Noribogaine	Quantitation LC/ESI-MS	Plasma (P) Blood (B)	Zorbax eclipse XD8 C8 (150 mm × 4.6 mm I.D.) Particle size, 5 µm	Solid–liquid Oasis-HLB cartridge after protein precipitation; elution with methanol	Ibogaine: 0.89 ng/mL (P) 1.78 ng/g (B) Noribogaine: 1 ng/mL (P) 2 ng/g (B)	Ibogaine: 94.2 % (P) 57% (B) Noribogaine: 96.9% (P) 62% (B)
Kontrimavičiūtė, <i>et al.</i> ³⁸	Ibogaine Noribogaine	Quantitation LC/ESI-MS	Urine	Zorbax eclipse XD8 C8 (150 mm × 4.6 mm I.D.) Particle size, 5 µm	Solid–liquid Oasis-HLB cartridge; elution with methanol	Ibogaine: 1.78 ng/mL Noribogaine: 2 ng/mL	Ibogaine: 70.0% Noribogaine: 81.7%

TLC, thin-layer chromatography; GC-FID, gas chromatography–flame ionization detection; GC-MS, gas chromatography–mass spectrometry; GC-EI-MS, gas chromatography–electron impact–mass spectrometry; GC-CI-MS, gas chromatography–chemical ionization–mass spectrometry; HPLC, high performance liquid chromatography; LC-APCI-MS, liquid chromatography–atmospheric pressure chemical ionization–mass spectrometry; LC-ESI-MS, liquid chromatography–electrospray ionization–mass spectrometry; LLOD, lower limit of detection; LLOQ, lower limit of quantitation.

release formulation of noribogaine as an anticraving medication for opiates and psychostimulants.⁴

Preclinical pharmacokinetics

Absorption

Studies in rats showed dose-dependent and gender-dependent bioavailability after oral route suggesting that ibogaine absorption, and/or first pass elimination, is non-linear.⁸ After oral administration of Iper-ton® capsules, containing 40 mg of natural extract of *T. iboga*, a substantial sex difference in rat brain and plasma concentrations of ibogaine was observed.³¹ These data were consistent with those of Pearl, et al.,⁴² reporting that plasma levels of ibogaine after oral administration were approximately threefold higher in female than in male rats, and the bioavailability of ibogaine was approximately twofold higher in female than in male.⁴² After oral administration of 5 and 50 mg/kg to rat, the bioavailability was 16% and 71% in female and 7% and 43% in male, respectively.⁴³

Distribution

An intriguing property of ibogaine is its prolonged duration of action when behavioral and neurochemical effects are identified after one or more days following oral, intraperitoneal (i.p.), or subcutaneous administration. Pharmacokinetics of ibogaine in rat were consistent with a two-compartment model, but the extremely high concentrations found in adipose tissues suggests the possibility of more complex pharmacokinetics.⁴⁴ One hundred times greater concentrations in fat and 30 times greater concentrations in brain, than in plasma found 1 h after administration were consistent with the highly lipophilic nature of ibogaine.⁴⁵ It was proposed that prolonged actions of ibogaine could be explained by adipose tissue reservoir with release and metabolism to active metabolite noribogaine over an extended period of time.^{45,46}

Another depot might be the platelets or other blood components, as concentrations of ibogaine were higher in the whole blood than in plasma.⁸ The concentrations of ibogaine and noribogaine have been measured in rat brain following both oral and i.p. administrations (40 mg/kg i.p., 50 mg/kg per os).^{47–49} The significance of micromolar interactions of ibogaine and noribogaine with various radioligand binding sites was related to the concentration of the parent drug and its metabolite in brain. Concentrations of these two drugs in rat cerebral cortex, striatum, brainstem, and cerebellum were measured 15 min, 1 and 2 h following drug administration. It was shown that ibogaine was rapidly detected in

brain following oral administration. Noribogaine was detected at the earliest time point (15 min) consistent with a first pass metabolism of the parent drug.⁴⁸ After i.p. and oral administrations of ibogaine in rat, maximum concentrations were 11–15 μM in the whole blood and the brain for ibogaine, and 21.9 μM in the whole blood and 9.8–11.3 μM in the brain for noribogaine. In the whole blood and in the brain, area under concentration-time curve (AUC) values were 9- and 1.8-times higher for noribogaine than for ibogaine, respectively. The AUC ratios (brain/whole blood) were equal to 2 for ibogaine and 0.4 for noribogaine.⁴⁹ These results report that noribogaine reaches significant concentrations in brain following both routes of administration in rat. Thus, the concentrations of noribogaine in brain may activate processes that cause the desired effects of suppressing opiate withdrawal signs and diminishing drug craving.

Metabolism

Ibogaine is metabolized by cytochrome P4502D6 (CYP2D6) into a major (active) metabolite – noribogaine.⁵⁰ An important aspect is that this isoform is subjected to polymorphic expression particularly in Caucasians. From in-vitro study using human liver microsomes, Obach, et al.⁵⁰ reported that two (or more) enzymes were involved in this reaction. These authors identified two kinetically distinguishable ibogaine *O*-demethylases involved in this reaction corresponding, to high (K_M , > 200 μM) and low (K_M , 0.1 μM) values of the apparent Michaelis constant. The importance of the route of administration has been underlined, indicating that the noribogaine/ibogaine concentration ratio in the bloodstream was higher when ibogaine is injected by the i.p. route rather than by the intravenous route.⁵¹ As well as, higher concentrations of ibogaine in plasma, brain, kidney, liver, and fat were observed following subcutaneous versus i.p. administration suggesting a substantial “first pass” effect after i.p. administration involving hepatic extraction.⁴⁵

It seems that noribogaine could be a safer and possibly more efficacious alternative to ibogaine as a medication for the treatment of various types of addiction.⁵¹

Elimination

The half-life of ibogaine in rat was 1–3 h.^{28,45,51} This elimination half-life could be underestimated since 3-h post-dose ibogaine concentrations remained very high in fat.⁴⁵ Ibogaine and noribogaine are excreted via the renal and the gastrointestinal tract (60–70% of the administered dose in 24 h in rat⁴³).

Pharmacodynamic studies in animals and mechanism of action

Primary and secondary pharmacology

Several reviews have reported the pharmacological profile of ibogaine.^{8,26,49,52} It has been shown that ibogaine and noribogaine interact with multiple binding sites within the central nervous system (CNS), including *N*-methyl-D-aspartate (NMDA) receptor-coupled ion channels, κ -opioid (κ_1 and κ_2), μ -opioid and σ_2 , serotonin (5-HT₂ and 5-HT₃), muscarinic (M₁ and M₂) receptors and monoamine uptake sites, and nicotinic acetylcholine receptors. The pharmacological profile of noribogaine is different from that of ibogaine.^{49,51–58} Ibogaine is more potent than noribogaine (i) in binding to the NMDA receptor in brain tissue^{49,54} and (ii) as a stimulator of the hypothalamic-pituitary-adrenal axis.^{54,55} Although ibogaine and 5-HT display chemical similarities, because both molecules contain an indole as part of their structure, noribogaine is much more potent than ibogaine in its ability to elevate extracellular 5-HT in the brain.⁵¹ Thus, this drug is 10-times more potent in binding to serotonin transporter and inhibiting reuptake of serotonin.^{49,51,53–55} Noribogaine is also (i) much more potent than ibogaine for binding to μ -opioid receptor and is a full μ -opioid agonist^{49,54,56–58} and (ii) more potent binding to κ_1 and less potent binding to κ_2 opioid receptors. Affinities of ibogaine and noribogaine to some of these receptors are reported in Table 2.⁴⁹ Although not apparent in binding studies, functional studies indicate significant activity of ibogaine as a non-competitive antagonist at the nicotinic acetylcholine receptor.⁴

Conflicting results were reported about the alteration of extracellular dopamine levels in the nucleus accumbens. According to Baumann, *et al.*,⁵¹ neither ibogaine nor its metabolite significantly altered dopamine levels, whereas Glick, *et al.*^{46,59} reported that these two drugs cause significant decreases in dopamine levels.

Signal transduction pathways were examined during several preclinical trials. The examination of discriminative stimulus effects of ibogaine and noribogaine in rats in relation to their concentrations in blood plasma and brain regions and to receptor systems suggested that noribogaine may be the major entity that produces the discriminative effect of ibogaine.⁴⁷ It has been reported that the observed increase in phosphoinositide hydrolysis by noribogaine should be accompanied by an activation of protein kinase C which mediated a variety of long-term changes and might be involved in the behavioral effects of ibogaine.⁶⁰ The selective increase in receptor-mediated inhibition of adenylyl cyclase activity caused by ibogaine and noribogaine might also be involved in the pharmacological activity of these compounds.⁶¹ Recently, it has been shown that the remedial effect of ibogaine as anti-addictive drug is mediated, at least partially, through an influence on energy metabolism.⁶² Among the recent proposals for ibogaine mechanisms of action is the activation of the glial cell line-derived neurotrophic factor (GDNF) pathway in the ventral tegmental area of the brain.⁶³ This work has principally been accomplished in preclinical ethanol research, where 40 mg/kg of ibogaine caused increase of RNA expression of GDNF in keeping with reduction of ethanol intake in the rat and absence of neurotoxicity or cell death. Short-term ibogaine exposure results in a sustained increase in GDNF expression, resulting in an increase in GDNF mRNA leading to protein expression and to the corresponding activation of the GDNF signaling pathway.⁶⁴

It was also shown that ibogaine and noribogaine may stimulate the secretion of corticosterone from the adrenal cortex and prolactin from the anterior pituitary.⁵¹ These two drugs also caused similar increase in plasma prolactin. Relevance of these physiological changes for primary or secondary pharmacology should be elucidated more in the future.

Table 2 Affinities of ibogaine and noribogaine to some receptors (according to Mash, *et al.*⁴⁹)

	Ibogaine	Noribogaine	Pharmacodynamic activity
	IC ₅₀ , μ M		
Serotonergic			
5-HT transporter (RTI-55 DAT sites)	0.59	0.04	Reuptake blocker
Opioidergic			
Mu (DAMGO)	11.0	0.16	Agonist
Kappa 1 (U69593)	25.0	4.2	Partial agonist (?)
Kappa 2 (IOXY)	23.8	92.3	Partial agonist (?)
Glutamatergic			
NMDA (MK-801)	5.2	31.4	Channel blocker

DAT, dopamine transporters; NMDA, *N*-methyl-D-aspartate.

Anti-addictive activity in animals

NMDA, opioid, and serotonin receptors have been targeted successfully for many years as anti-addictive treatment of opioid and/or cocaine addiction.^{65,66} Activities of both ibogaine and noribogaine on these receptors provided a biological plausibility to expect anti-addictive efficacy for ibogaine in human also. Initial findings, suggestive of the efficacy of ibogaine in animal models of addiction, including diminished opioid self-administration and withdrawal^{67–69} and diminished cocaine self-administration,⁷⁰ were published in late 1980s and in early 1990s.

Animal models of addiction were used to study the activity of ibogaine in the treatment of drug dependence. The administration of ibogaine reduced self-administration of cocaine, morphine, heroin, alcohol, and reduced nicotine preference.⁸ The decrease in cocaine consumption has been described in mice after i.p. administration of two 40 mg/kg dose at 6 h interval⁷¹ and in rat after i.p. administration of 2.5–80 mg/kg given as single or repeated doses (daily or weekly, $n = 3$).^{67,70,72} According to Cappendijk and Dzoljic, the maximum effects were observed when ibogaine was given weekly for 3 weeks.⁷⁰ The decrease in opiate consumption has been described after administration of 2.5–80 mg/kg ibogaine in morphine- and heroin-dependent rat.^{67,72,73}

Ibogaine also eliminates some of the signs of opiate withdrawal precipitated by naloxone or naltrexone in morphine-dependent rats given 20, 40, or 80 mg/kg ibogaine i.p.^{68,74} and monkeys given 2 or 8 mg/kg ibogaine subcutaneously.^{75,76} However, Sharpe and Jaffe⁷⁷ failed to report that ibogaine administered subcutaneously attenuated naloxone-precipitated withdrawal in rat receiving 5, 10, 20, and 40 mg/kg of ibogaine. Conflicting results were observed in mice. At doses ranging from 40 to 80 mg/kg i.p., a reduced naloxone-precipitated jumping in morphine-dependent mice was observed^{77,78}; however, opposite effects were found after a 30 mg/kg i.p. dose.⁷⁹ These discrepancies might be related to ibogaine administration: before^{77,78} or after⁷⁹ naloxone administration.

Although ibogaine has diverse effects on the CNS, the pharmacological targets underlying the physiological and psychological actions of ibogaine are not completely understood.

Preclinical safety studies

Several safety studies were performed during preclinical development. These studies raised several

safety concerns, mainly neurotoxicity and possible cardiotoxicity.

Multiple laboratories have reported on the degeneration of cerebellar Purkinje cells in rat receiving i.p. administration of ibogaine at a dose of 40–100 mg/kg.^{51,74,80} These include abnormal motor behavior (such as tremors, ataxia) related to histologically proven neurotoxicity.⁸⁰ Single-dose investigations showed that a 25 mg/kg i.p. dose was found to correspond to a no-observed-adverse-effect-level (NOAEL).⁸¹ Helsley, *et al.* observed no evidence of neurotoxicity in a study where rats received 10 mg/kg of ibogaine per day for 60 days.⁸² However, the neurotoxic effects of ibogaine may occur at levels higher than those observed to have effects on opioid withdrawal and self-administration. The monkey appears to be less sensitive to potential ibogaine neurotoxicity than the rat.⁴ Mash, *et al.* observed no evidence of neurotoxicity in monkeys treated for 5 days with repeated oral doses of ibogaine of 5–25 mg/kg or subcutaneously administered doses of 100 mg/kg.⁴ Another species difference in sensitivity is the mouse, which unlike the rat showed no evidence of cerebellar degeneration at a 100 mg/kg i.p. dose of ibogaine.⁸³

Animal studies showed certain cardiotoxicities. Observed cardiotoxicity could be dose dependent. No changes in resting heart rate or blood pressure were found at a dose of ibogaine of 40 mg/kg i.p., which has been used in drug withdrawal or self-administration studies. Higher doses of ibogaine (100 and 200 mg/kg) decreased the heart rate without an effect on blood pressure.⁸⁴ However, Binienda, *et al.*⁸⁵ found a significantly decreased heart rate in rats given ibogaine 50 mg/kg i.p. The lethal dose 50% of ibogaine was 145 mg/kg i.p. and 327 mg/kg intragastrically in the rat, and 175 mg/kg i.p. in the mouse.²⁸

In conclusion, preclinical development showed that ibogaine is acting on several mediators in CNS that have been targeted in treatment of drug-dependence. Neurotoxicity and cardiotoxicity are safety concerns to be investigated further. No sufficient long-term safety non-clinical studies are available. All these data make further investigation of ibogaine's activity as potential therapeutic agent biologically plausible.

Clinical pharmacokinetic and pharmacodynamic studies

Clinical studies

Clinical development of ibogaine has continued for some decades. Development was governed by

several sponsors handed over management from one hand to other. Development was carried by several separate academicians and companies.

The first pharmacodynamic studies of ibogaine have been performed during 1901–1905. First anti-addictive attempts were done by Harris Isbell in 1955, administering doses of ibogaine of up to 300 mg to eight already detoxified morphine addicts at the United States. Addiction Research Centre in Lexington, Kentucky.⁸ In 1962–1963, Lotsof administered ibogaine at the dose of 6–19 mg/kg, to 19 individuals including seven subjects with opioid dependence who noted an apparent effect on acute withdrawal symptomatology.^{18,19} In 1967–1970, the World Health Assembly classified ibogaine with hallucinogens and stimulants as a “substance likely to cause dependency or endanger human health”. In 1970, the US Food and Drug Administration (FDA) classified ibogaine as a Schedule I Controlled Substance, along with other psychedelics such as LSD and mescaline. The International Olympic Committee banned ibogaine as a potential doping agent. Thus, sales of Lambarène® were stopped in France.⁹ Since that time, several countries, including Sweden, Denmark, Belgium, Switzerland, and recently (since March 2007) France, have banned the sale and possession of ibogaine.

The available data from private clinics described in scientific reports, where ibogaine has been used for informal addiction treatment, stated that ibogaine has been taken orally at an average dose of 19.3 ± 6.9 mg/kg.^{86,87} Another study reported six heroin-addicted individuals and one subject who were addicted to codeine treated with ibogaine at doses ranging from 700 to 1800 mg.⁴⁰

From 1989 to 1993, treatments were conducted outside of conventional medical settings in the Netherlands involving the International Coalition of Addict Self-Help, Dutch Addict Self Help, and NDA International.^{8,88} In 1991, NIDA Medication Development Division began its ibogaine project. This initiative was based on case reports and preclinical evidence suggesting possible efficacy. The major objectives of the ibogaine project were preclinical toxicological evaluation and development of a human protocol. In August 1993, FDA Advisory Panel meeting formally considered Investigational New Drug Application filed by Dr Deborah Mash, Professor of Neurology at the University of Miami. Approval for human trials was given with 1, 2, and 5 mg/kg of ibogaine dosage levels. The Phase I dose escalation study began in December 1993, but activity was eventually suspended.^{4,8} From October 1993 to December 1994, phase I/II protocols were discussed by the NIDA and fixed doses of ibogaine of

150 and 300 mg versus placebo for the indication of cocaine dependence were proposed.^{8,89} The next year, a NIDA ibogaine review meeting decided to end the ibogaine project but to continue to support some preclinical research on iboga alkaloids. A fatality occurred during a heroin detoxification treatment of a 24-year-old women in the Netherlands in June 1993. This incident was a significant factor in the NIDA decision not to fund a clinical trial of ibogaine in 1995.⁸ But the drug-addicted persons continue taking purified ibogaine hydrochloride powders or a whole plant extract that contains an unidentified number of other biologically active compounds. Some practically applied recommendations instruct taking between 2 and 6 g of powdered iboga.⁹⁰

Some clinical experiences were gained during mid 1990s to 2001. At that time, ibogaine was available in alternative settings and studies based on a conventional medical model were carried out in Panama and in St Kitts. Informal protocols were developed in the United States, Slovenia, Britain, the Netherlands, and the Czech Republic. The ibogaine mailing list began in 1997 and heralded an increasing utilization of the Internet within the ibogaine medical subculture.

In early 2006, the creation of a non-profit foundation addressing the issue of providing ibogaine for the purpose addiction interruption within establishment drug treatment care was formed in Sweden (Stiftelsen Iboga's web site, accessed march 2007).

Pharmacokinetics

Pharmacokinetic data relative to ibogaine in human are limited.^{8,49,56,91} Most of these studies have been carried out in drug-dependent patients. Following single oral doses of ibogaine (500–800 mg) to individual subjects, maximum ibogaine and noribogaine blood concentrations of 30–1250 ng/mL and 700–1200 ng/mL were obtained approximately 2 and 5 h after drug administration, respectively.^{49,56} Thereafter, ibogaine was cleared rapidly from the blood, whereas noribogaine concentrations remained high. Indeed, concentrations of noribogaine measured at 24 h post-dose were in the range of 300–800 ng/mL whereas those of ibogaine were about 100 times lower. From blood concentration-time profiles of ibogaine published by Mash, *et al.*,^{49,56} after an oral dose of 800 mg, the steady-state volume of distribution uncorrected for bioavailability was about 13 l/kg and the half-life of the terminal part of the curves was 4–7 h. Ibogaine being metabolized by the CYP2D6 into noribogaine, the pharmacokinetic profile of this drug was different in extensive and poor metabolizers. After single oral doses of ibogaine (10 mg/kg), maximum concentrations of noribogaine

were nine times lower in poor metabolizers ($n = 3$) than in extensive metabolizers ($n = 24$), whereas maximum concentrations of ibogaine were about 18% higher comparing to extensive metabolizers. This gap reflects speculation that conversion rate of the parent compound to noribogaine in CYP2D6 deficient subjects may reflect the metabolic contribution of other cytochromes (CYP2C9, CYP3A4). The blood AUC values, poor metabolizers versus extensive metabolizers, were almost three times higher for ibogaine and four times lower for noribogaine. These AUC levels were more representative for understanding systemic exposures in extensive and poor metabolizers. In extensive metabolizers, the blood AUC ratio, noribogaine/ibogaine, was approximately 3. Thus, the contribution of noribogaine to the total pharmacodynamic effect of the parent drug was significant. The calculated terminal half-life of ibogaine in this study was 7.45 h in extensive metabolizers.

In a recent study, Kontrimavičiūtė, et al.⁹¹ reported for the first time the tissue distribution of ibogaine and noribogaine, in a subject dead after a poisoning involving ingestion of root bark of the shrub *T. iboga*. The highest concentrations of ibogaine and noribogaine were found in spleen, liver, brain, and lung. The tissue/sub-clavian blood concentration ratios averaged 1.78, 3.75, 1.16, and 4.64 for ibogaine and 0.83, 2.43, 0.90, and 2.69 for noribogaine, for spleen, liver, brain, and lung, respectively. Very low concentrations of the two drugs were found in the prostatic tissue. No compounds

were detected in the cardiac tissue. Both ibogaine and noribogaine are secreted in the bile and cross the blood–brain barrier.

Results are summarized in Table 3.

Pharmacodynamic effects

Some case-report studies showed that ibogaine is active as psychotropic agent with possible anti-addictive activity in acute opioid withdrawal.^{4,41,86,87} After administration of ibogaine, individuals can experience (i) certain subjective new experience and (ii) reductions of drug craving and withdrawal signs and symptoms.

Subjective new experiences described by patients treated with ibogaine Preliminary data shows that patients experience several different phases that may be categorized into acute, evaluative, and residual stimulation stages (Figure 3).⁸

The first phase (acute phase) is experienced within first 1–3 h after exposure and lasts 4–8 h. During this phase, patients report panoramic delivery of long-term memory, mainly visual; “visions” or “waking dream” states experiencing contact with transcendent beings, passage along a lengthy path, floating, etc. Although visual experiences are not reported by all patients and seem depend of drug exposure, it is also noticed that they were associated and enhanced with eye closure. Unfortunately, difference between these dreams and hallucinations are not clear enough.

Table 3 Pharmacokinetic parameters from clinical studies

		Extensive metabolizers ($n = 24$) ⁴⁹	Poor metabolizers ($n = 3$) ⁴⁹
Ibogaine doses	500–800 mg	10 mg/kg	10 mg/kg
Ibogaine			
$t_{\max}$, h	2	1.7	2.5
$C_{\max}$, ng/mL	30–1250	737	896
V_{ss}/F , l/kg	13	—	—
$t_{1/2}$ (last phase), h	4–7	7.5	—
AUC _{0–24h} , ngxh/mL	—	3936	11471
Tissular distribution (tissue/blood concentration ratios)	Spleen: 1.78 Liver: 3.75 Brain: 1.16 Lung: 4.64 Bile: 1.97	—	—
Noribogaine			
$t_{\max}$, h	5	6.2	3.2
$C_{\max}$, ng/mL	700–1200	949	105
C_{24h} , ng/mL	300–800	—	—
AUC _{0–24h} , ngxh/mL	—	14705	3648
Tissular distribution (tissue/blood concentration ratios)	Spleen: 0.83 Liver: 2.43 Brain: 0.90 Lung: 2.69 Bile: 0.54	—	—

n , number of subjects; $C_{\max}$, maximum concentration; $t_{\max}$, time of $C_{\max}$; C_{24h} , concentration 24 h post-dose; AUC_{0–24 h}, area under concentration-time curve; V_{ss} , steady-state volume of distribution; $t_{1/2}$, half-life.

Opiate withdrawal	Reduction of drug craving	Reduction of drug withdrawal	Reduction of depression and drug craving (up to one month)	Reported cessation of drug use (up to more than 1 year)*
Personal new experience	<i>Acute</i> phase with "oneiric" experiences (onset: 1-3 h, duration: 4-8 h)	<i>Evaluative</i> phase with "neutral" and "reflective" emotional tone (onset: 4-8 h, duration: 8-20 h)	<i>Residual Stimulation</i> phase with return of normal allocation of attention (onset: 12-24 h, duration: 24-72 h)	

* Reported cessation from the sample of 41 individuals: nine individuals were treated twice and one was treated three times for a total of 52 treatments. Fifteen (29%) of the treatments were reportedly followed by cessation drug use for less than 2 months, 15 (29%) for at least 2 months and less than 6 months, 7 (13%) for at least 6 months and less than one year, 10 (19%) for a period of greater than one year (8, 89, 93).

Figure 3 Clinical pharmacodynamic effects after ibogaine administration.

The second phase (evaluative phase) starts approximately 4–8 h after ingestion and lasts 8–20 h. During this phase, dreams decreased slowly and the emotional tone is generally described as neutral and reflective. Patients reflect that their attention is focused on inner subjective experiences (i.e., by evaluating the experiences of the acute phase).

During these two first phases, patients tend to stay focused on their experiences and avoid any external distraction.

The third phase (residual stimulation phase) starts 12–24 h after exposure and lasts 24–72 h. Patients regain normal attention to the external environment. Subjective psychoactive experience lessens, remaining with mild residual subjective arousal or alertness. Decrease in the need to sleep for several days to weeks can be observed.

Reductions of withdrawal signs and symptoms, drug craving and depression After administration of 6–29 mg/kg dose of ibogaine, acute reduction in drug craving and opiate withdrawal signs and symptoms are observed in 1–2 h. Resolution of withdrawal was observed during 1 week, reduction of craving and depression – 1 month after exposure.

Opiate physical dependence is assessed usually by discontinuation of opiate treatment (spontaneous withdrawal) or by antagonist-precipitated withdrawal.⁴⁹ Usually, acute withdrawal syndrome in case of heroin addiction may begin approximately 8 h after the last heroin dose, peaks in intensity at 24–28 h, and subsides within 7–10 days. In one of the opiate (heroin or methadone) addiction studies including 32 patients, rapid detoxifications of these patients was assessed after single-dose ibogaine treatment (10 mg/kg). Results are summarized in Table 4. The post-ibogaine Objective Opiate Withdrawal Scale (OOWS) blinded rating obtained 10–

12 h and 24 h after ibogaine administration (i.e., 24 and 36 h after the last dose of opiate, respectively) was statistically lower than the rating obtained 1 h before ibogaine administration. The OOWS mean total score decreases from approximately 5.6 to 1.1 and 1.9, 12, and 24 h following ibogaine administration, respectively. Authors noticed that objective signs of opiate withdrawal were rarely seen and none were exacerbated at later time points.

A second measurement used was "self-reports of withdrawal symptoms according to Opiate-Symptom Checklist" (OP-SCL). This "discomfort" measurement showed statistically significant decreases in mean scores: from approximately 21 (score observed 24 h before ibogaine treatment) to 12 shortly after recovery from ibogaine treatment (<72 h) and down to 7 (at program discharge, approximately 6–9 days later).

Impressive success of single dose of ibogaine detoxification process was noticed as well as the fact that many of the patients were able to maintain abstinence over the months following detoxification.⁴⁹ This relatively small study suggests that methadone withdrawal was not more difficult to detoxify than heroin withdrawal. Speculation that long-acting metabolite noribogaine may account for the efficacy of ibogaine can be done.

Craving is an important symptom reported by opiate-dependent subjects during the early stages of withdrawal contributing to continued drug use.^{49,92} Craving symptoms for opiates could be evaluated by using the "Heroin Craving Questionnaire scales (HCQN-29)". Thirty-six hour post-ibogaine treatment, the mean scores on five measures about specific aspects of drug craving (including urges, thoughts about drug of choice, or plans to use the drug) show significant decreases and lasted at program discharge.

Evaluation of patients using Beck Depression Inventory scores showed also significant reduction of scores both at program discharge and at 1-month follow-up assessments.^{49,56}

Subjects undergoing cocaine detoxification also reported significant decrease in drug-craving 36 h post-ibogaine treatment and at discharge for three of the five category scales of the Cocaine Craving Questionnaire (CCQN)-45 (anticipation of positive outcomes, relief of negative states, and lack of control).

There is only limited retrospective experience in long-term outcomes (Figure 3).^{8,88,93} No clear negative or positive conclusions could be drawn. It seems that relapses could be attempted with ibogaine re-challenge, as this was done several times in anecdotal cases.

It seems that pharmacodynamic effects experienced by patients varied and may be related to dose, bioavailability, and interindividual variabilities.⁸ Sequential pattern of clinical pharmacodynamic effects could be summarized as presented in Figure 3.

Clinical safety

Neurotoxicity observed in animal studies was also noticed in human studies (e.g., effects on postural stability, body tremor, and appendicular tremor). In 1994, a fatal case of woman treated with ibogaine was reported. Fifteen months before her death, this woman had undergone four separate treatments with ibogaine in rather high dosages (ranging from 10 to 30 mg/kg). Death was not attributed to ibogaine but was related to mesenteric arterial thrombosis related to chronic cellulitis.^{4,8}

Similar to the findings in animals, some cardiac side-effects were also observed during clinical investigations.^{8,94} Thirty-nine patients dependent

on cocaine and/or heroin, who received fixed oral doses of ibogaine of 500, 600, 800, or 1000 mg, were monitored. Six subjects exhibited some significant decrease of resting pulse rate; one of them evidenced a significant decrease in blood pressure (attributed to a transient vasovagal response). No evidence of electrocardiogram abnormalities was showed. There were hypotensive episodes (responsive to volume repletion) noticed during ibogaine therapy in some cocaine-dependent subjects.⁴⁹

The safety of ibogaine was also evaluated in more than 150 drug-dependent subjects receiving 8, 10, or 12 mg/kg ibogaine.⁴⁹ The most frequent side-effects encountered were nausea and mild tremor, and ataxia earliest after drug administration. A hypotension was observed in some cocaine-dependent subjects, who required close monitoring of blood pressure. No other significant adverse events were seen under the study conditions; and, therefore, there are no clear evidences till now that there are big issues in tolerance after single dose of ibogaine.

In conclusion, clinical development could be considered as started only and needs essential exploratory program first.

Main unanswered questions

Experience available in public domain suggests that ibogaine might have some activity in anti-addiction treatment. Although data seems quite promising, several issues remain to be elucidated first before moving further towards controlled pivotal clinical trials. Four major product development issues to be solved relates to the areas of pharmaceutical formulation development and starting clinical exploratory studies:

- 1) Is ibogaine pharmaceutical formulation developed enough to ensure proper constant composition form certain active ingredients?

Table 4 Effects of single-dose ibogaine (10 mg/kg) on opiate withdrawal signs

	<i>Time after the last opiate dose, h</i>	<i>Time after the ibogaine dose, h</i>	<i>OOWS</i>	<i>OP-SCL</i>	<i>HCQN-29^a</i>	<i>BDI</i>
Before ibogaine treatment			5.6 (1 h)	21 (24 h)	3.26–4.88	16.9
	24	10–12	1.1*			
	36	24	1.9*			
		36			1.57–3.67	10.4
		<72 h		12*		
		6–9 days		7*		
Discharge					1.22–2.85***	3.0**
1-month follow-up						2.29**

OOWS, Objective Opiate Withdrawal Scale; OP-SCL, Opiate-Symptom Checklist; HCQN-29, Heroin Craving Questionnaire scales (subscales: desire to use, intention to use, anticipation of positive outcomes, relief of negative states and lack of control); BDI, Beck Depression Inventory scores.

^aAccording to the subscale.

* $P < 0.05$; ** $P < 0.0005$; *** $P < 0.0001$.

- 2) What is ibogaines' pharmacodynamic activity in controlled exploratory trial in drug-dependent stabilized subjects?
- 3) What is ibogaines' potential for abuse by drug-dependent subjects (in both pharmacodynamic and economic measurements)?
- 4) What is the most rational dosage range to be studied in dose-response studies in treatment of some drug dependences (first, in opiate and/or cocaine dependencies)?

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Conclusion

Experience available in public domain suggests that ibogaine might have some activity in anti-addiction treatment, but current data are not sufficient to do further in development. Data gathered during more than 100 years of pharmaceutical, non-clinical, and clinical developments need to be validated. Good laboratory and clinical practice environment is essential for future investigations. Several major objectives of preclinical and clinical investigations should focus on core-identified questions first.

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